Remarks

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for the amendments to claims 14, 15, 19, 31 and 40 may be found in the specification throughout the Examples, specifically at pages 54-56, 62-63, 68-73, and 74-76 (including Table 5 at page 75), and in Figures 16, 18 and 20. The amendment to claim 104 is sought solely to delete subject matter from this claim. Accordingly, the present amendments do not add new matter, and their entry and consideration are respectfully requested.

I. Status of the Claims

By the foregoing amendments, claims 14, 15, 19, 31, 40 and 104 have been amended. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 14-51, 65-76 and 81-104 are pending in the application, with claims 14, 19, 31 and 40 being the independent claims.

II. Summary of the Office Action

In the Office Action, the Examiner has made six rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

III. The Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action at page3, the Examiner has rejected claims 89-91 and 97-101 under 35 U.S.C. § 112, first paragraph, for alleged lack of sufficient written description. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that "there is no literal support . . . in the specification as originally filed" for the recitations of "at least one isolated recombination protein" wherein the protein is IHF, Cre, Xis, Int, FIS, etc. *See* Paper No. 25 at page 3, final paragraph. Thus, the Examiner concludes, these recitations in claims 89-91 and 97-101 "are impermissible NEW MATTER" (*id.*; emphasis in original). Applicants respectfully disagree.

First, the use of a variety of recombination proteins, including those specifically recited in the rejected claims, is fully described in the specification at pages 33-40. Second, the preparation and isolation of at least three recombination proteins (Int, IHF and Xis) is specifically described in the Examples, including, *inter alia*, at pages 52-54, at pages 57-62, in Table 2 at page 67, and at pages 73-74. Hence, it is incorrect to contend that "there is no literal support" in the present specification for the use of isolated recombination proteins, since such proteins are fully described and exemplified.

In any event, it is irrelevant for purposes of 35 U.S.C. § 112 whether or not a given claim limitation is literally supported in the specification. Applicants remind the Examiner that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention . . . . the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd.

Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification . . . ." *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

As noted above, the present specification describes and exemplifies a variety of isolated recombination proteins, including those recited in claims 89-91 and 97-101. Irrespective of this explicit description, however, a sufficient written description of such methods does not require *in haec verba* description of the isolated proteins recited in these claims when, as here, one of ordinary skill could readily appreciate that Applicants possessed what they claim as of the filing date of the application. In the present case, Applicants have provided exemplary disclosure of the isolation of at least three recombination proteins. One of ordinary skill would have no reason to doubt that other recombination proteins, *e.g.*, those recited in claims 89-91 and 97-101, could be similarly prepared and isolated, particularly since such isolated proteins are clearly contemplated and described in the present specification. Hence, under *Parks* and *Alton*, the present specification clearly provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application.

In view of the foregoing remarks, Applicants respectfully assert that claims 89-91 and 97-101 are fully described in the specification as filed. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

IV. The Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at page 4, the Examiner has rejected claims 14-51, 65-76 and 81-104 under 35 U.S.C. § 112, second paragraph, for being allegedly indefinite. Applicants respectfully traverse this rejection.

A. The Recitation of "Purified"

The Examiner first contends that claims 14-51, 65-76 are indefinite for reciting that the ribosomal proteins used are "purified." Specifically, the Examiner has suggested that the claims be amended "to clearly indicate to what extent the ribosomal proteins of the inventions [sic] have to be isolated from their environment in order to satisfy the limitation of being 'purified'." Paper No. 28 at page 4, third paragraph. Applicants respectfully disagree with these contentions. However, to expedite prosecution and not in acquiescence to this portion of the rejection, the recitation of "purified" has been deleted from independent claims 14, 19, 31 and 40, from which the remaining claims ultimately depend. Hence, reconsideration and withdrawal of this portion of the rejection are respectfully requested.

B. The Recitation of "Said First Or Second Nucleic Acid Molecule"

The Examiner has next rejected claims 102-103 as being indefinite for reciting "said first or second nucleic acid molecule," which is said to lack sufficient antecedent basis in claims 31 and 40 from which claims 102 and 103 depend. By the foregoing amendments, claims 31 and 40 have been amended to recite "at least a first nucleic acid molecule and at least a second nucleic acid molecule." Thus, antecedent basis for this recitation in claims 102 and 103 is found in claims 31 and 40. Accordingly, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

C. The Recitation of "Said Fourth Nucleic Acid Molecule"

Finally, the Examiner has rejected claim 104 as being indefinite for reciting "said fourth nucleic acid molecule," which is said to lack sufficient antecedent basis in claims 14, 19, 31 and 40 from which claim 104 depends. By the foregoing amendments, claim 104 has been amended such that it no longer depends from claims 14, 19, 31 and 40. Instead, claim 104 now depends solely from claim 15, which recites a "fourth nucleic acid molecule." Thus, antecedent basis for this recitation in claim 104 is found in claim 15. Accordingly, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

D. Summary

In view of the foregoing remarks, Applicants respectfully assert that the present claims particularly point out and distinctly claim the subject matter regarded by Applicants

as their invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, therefore are respectfully requested.

V. The Rejections Under 35 U.S.C. § 102(b) Are Traversed

In the Office Action at pages 5-8, the Examiner has rejected claims 31-32, 36, 38-51, 65-72, 74-76, 87-89, 91-95, 98 and 100-103 under 35 U.S.C. § 102(b) as being anticipated by Nash *et al.* (*Meth. Enzymol. 100*:210-216 (1983)) (Doc. No. AS34, of record; hereinafter "Nash"). In addition, the Examiner has rejected claims 40-51 and 89-103 under 35 U.S.C. § 102(b) as being anticipated by Abremski *et al.* (*J. Biol. Chem. 259*:1509-1514 (1984)) (Doc. No. AS1, of record; hereinafter "Abremski I") and Abremski *et al.* (*J. Biol. Chem. 257*:9658-9662 (1982)) (Doc. No. AR1, of record; hereinafter "Abremski II"). Applicants respectfully traverse these rejections, and reiterate and incorporate herein by reference the remarks concerning these same rejections that were made in Applicants' replies filed in the present matter on March 8, 2001, and on September 3, 2002. Applicants also wish to offer the following additional remarks.

As an initial matter, Applicants note that the Examiner has stated that "[t]his rejection is maintained for reasons of record in Paper No. 8, mailed 11/8/00 and extended to newly added claims 80 and 88." Paper No. 25 at page 6, lines 1-2. Applicants wish to remind the Examiner that claim 80 is not currently pending in the present application, having been previously cancelled, and that claim 88 is not "newly added," having been entered in Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed on March 8, 2001. Accordingly, the contention at the top of page 6 of Paper No. 25 is in error; correction on the record is respectfully requested.

Applicants note that independent claims 31 and 40, and thus the remaining claims that depend directly or ultimately therefrom, recite methods comprising forming a mixture *in vitro* between at least a first nucleic acid molecule and at least a second nucleic acid molecule, and incubating the mixture under conditions such that a recombination reaction takes place between recombination sites on the first and second molecules. Hence, the present claims are drawn to *inter*molecular recombination reactions, that take place between two or more nucleic acid molecules. In contrast, the methods disclosed in Abremski I and Abremski II are limited to *intra*molecular recombination reactions, that take place *within* a single nucleic acid molecule. *See, e.g.*, Abremski I at page 1510, col. 1, particularly at second full paragraph, lines 2-5; and Abremski II at page 9659, col. 1, particularly at lines 4-6, and in Figure 1 at page 9659. With regard to Nash, Applicants note that claims 31 and 40 both recite methods for *enhancement of* recombinational cloning. In contrast, Nash does not disclose that the methods disclosed therein provide any particular enhancement to cloning reactions. Hence, Nash, Abremski I and Abremski II do not disclose each and every element of the presently claimed invention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As noted above, Nash, Abremski I and Abremski II do not expressly or inherently disclose every element of the present claims. Accordingly, the presently claimed invention is not anticipated by Nash, Abremski I or Abremski II, and Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) over these references be reconsidered and withdrawn.

VI. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at pages 8-10, the Examiner has rejected claims 14-51 and 65-104 under 35 U.S.C. § 103(a) as being unpatentable over Hartley *et al.* (U.S. Patent No. 5,888,732; hereinafter "Hartley") in view of Nash, or Abremski I, or Abremski II. Applicants note that claims 77-80 are not pending in the present application, having been previously cancelled. Hence, the rejection of claims 77-80 on these grounds is in error, and correction of this issue on the record is respectfully requested. Applicants respectfully traverse this rejection as it may apply to the remaining claims, and reiterate and incorporate herein by reference the remarks made in Applicants' previous replies concerning this rejection. Applicants also wish to provide the following additional remarks.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

As noted in Applicants' previously filed reply, and as the Examiner has acknowledged, Hartley does not disclose, suggest or contemplate the specific limitations of using ribosomal proteins in the methods disclosed therein. As the Examiner has also previously acknowledged (and again acknowledges in the present Office Action), Hartley does not even teach the use of crude cellular extracts in the recombination methods disclosed therein. Hence, whether or not ribosomal proteins are present in crude cellular extracts is of no moment with respect to the disclosure of Hartley, since Hartley does not disclose the use of such extracts.

Moreover, the Examiner's apparent contention that Hartley is suitable as a primary reference because this reference "[does not] teach that such extracts cannot be used" is irrelevant. Applicants respectfully remind the Examiner that the *explicit* disclosure and suggestion required for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Thus, the only relevant consideration in considering a proper obviousness rejection is what Hartley explicitly *does* disclose or suggest, not what Hartley does *not* disclose or suggest.

These deficiencies are not cured by the disclosures of Nash, Abremski I and Abremski II which, as noted above, do not disclose, suggest, or otherwise contemplate all of the elements of the presently claimed invention. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See Fine*, 5 USPQ2d at 1598 (Fed. Cir. 1988). Thus, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully contend that claims 14-51, 65-76 and 81-104 are not rendered obvious by the cited references. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

VII. The Double Patenting Rejection

In the Office Action at page 11, the Examiner has rejected claims 14-51 and 65-88 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of Hartley. Applicants again note that claims 77-80 are not pending in the present application, having been previously cancelled. Hence, the rejection of claims 77-80 on these grounds is in error, and correction of this issue on the record is respectfully requested. Applicants respectfully traverse this rejection as it may apply to the remaining claims, and reiterate and incorporate herein by reference the remarks made in Applicants' previous replies concerning this rejection. Applicants also wish to provide the following additional remarks.

As discussed above, and as the Examiner has conceded, Hartley does not disclose or suggest the use of crude cell extracts in the methods disclosed in that reference. It therefore follows *a fortiori* that Hartley does not disclose or suggest the use of ribosomal proteins in the methods claimed therein. Claims 29-73 of Hartley are drawn to a generic method that encompasses the present invention as a species. However, the disclosure of a genus does not necessarily render obvious any species that happens to fall within it. *See In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In making this rejection, the Examiner has not provided evidence as to why the skilled artisan would specifically use ribosomal

proteins in recombination reactions (which, as the Examiner has conceded, Hartley does not disclose) based solely on the disclosure of Hartley. Absent such evidence, Hartley cannot be used in an obviousness-type double patenting rejection, since there is no evidence that the presently claimed invention would have been obvious over Hartley.

Moreover, the Examiner's offhand dismissal of Applicants' arguments concerning this rejection (*see* Paper No. 25 at page 11, final paragraph) does not properly consider the issue at hand. Contrary to the Examiner's contentions in the present Office Action, Applicants' arguments presented in the previous reply concerning this rejection related solely to the disclosure contained in Hartley, and did not reiterate arguments made with respect to the obviousness rejection over Hartley in view of Nash or Abremski I/Abremski II. Unlike the rejection under 35 U.S.C. § 103(a), the present obviousness-type double-patenting rejection has been based solely on the disclosure of Hartley. Applicants therefore presented arguments as to why Hartley is insufficient to support this rejection, rather than reiterating any argument made with respect to Hartley in view of Nash, Abremski I and/or Abremski II. Indeed, Applicants went further in the previous reply, presenting a basis in the case law under *Baird* and *Jones* (as is also noted above) why Hartley cannot support this rejection. Hence, the Examiner is respectfully requested to consider the full scope of Applicants' comments in reconsidering this rejection.

In view of the foregoing remarks, Applicants respectfully assert that the presently claimed invention is patentably distinct over the claims of Hartley. Reconsideration and withdrawal of the obviousness-type double patenting rejection are therefore respectfully requested.

VIII. Other Matters

Applicants again note that they have not received the Examiner-initialed copy of the Forms PTO-1449 submitted with Applicants' IDS filed on September 18, 2000, indicating that courtesy copies of unlocated documents AT1, AS4, AT4, AR5, AR9, AR19, AT21, AS22, AS24, AS26, AS29, AR32, AS32, AR35, AT36, AS38, AT40, AR46, AS46, AR47, AR49, AS49, AR50, AS52, AR53, AR54, AR57, AT58 and AS59-AS62 have been considered. In Paper No. 25 at pages 2-3, the Examiner contends that the Form PTO-1449 and the cited references filed with this IDS were not received, nor were the courtesy copies of the Form PTO-1449 and references that were filed on March 8, 2001. The Examiner has further stated that, in order for these references to be considered, "it will be necessary to send in a PTO Form 1449 corresponding to the references as well as additional copies of the references." Paper No. 25 at page 3, lines 6-7.

Applicants note that these documents were originally submitted to the Office on September 18, 2000. Upon being informed by the Examiner that the copies of these documents could not be located in the USPTO file wrapper for this application, Applicants submitted courtesy copies of these documents on March 8, 2001; however, these courtesy copies have also apparently not been matched with the USPTO file wrapper of the present application. Applicants therefore will attempt to locate these references in the USPTO or, alternatively, will re-submit courtesy copies of these references and the accompanying IDS and Form PTO-1449 directly to the Examiner in the very near future. However, since the re-submission of these documents will represent the third time that these same references have been provided to the Office, at considerable expense to Applicants, the Examiner's

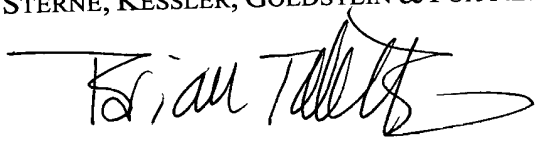
assistance in entering these references into the official file wrapper of the present application, once received in the Art Unit, is respectfully requested.

IX. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Version with markings to show changes made

Claims 14, 15, 19, 31, 40 and 104 have been amended as follows:

14. (Three times amended) A method for cloning or subcloning one or more desired nucleic acid molecules comprising

(a) forming a mixture by combining *in vitro*

(i) one or more first nucleic acid molecules comprising one or more desired nucleic acid segments flanked by at least two recombination sites, wherein said recombination sites do not recombine with each other;

(ii) one or more second nucleic acid molecules each comprising at least two recombination sites, wherein said recombination sites do not recombine with each other;

(iii) at least one recombination protein; and

(iv) at least one [purified] ribosomal protein; and

(b) incubating said mixture under conditions sufficient to transfer one or more of said desired segments into one or more of said second nucleic acid molecules, thereby producing one or more desired third nucleic acid molecules.

15. (Three times amended) The method of claim 14, further comprising:

(c) forming a mixture by combining *in vitro*

(i) one or more of said third molecules comprising said desired segments flanked by two or more recombination sites, wherein said recombination sites do not recombine with each other;

(ii) one or more different fourth nucleic acid molecules each comprising two or more recombination sites, wherein said recombination sites do not recombine with each other;

(iii) at least one recombination protein; and

(iv) at least one [purified] ribosomal protein; and

(d) incubating said mixture under conditions sufficient to transfer one or more of said desired segments into one or more different fourth nucleic acid molecules, thereby producing one or more different fifth nucleic acid molecules.

19. (Three times amended) A method for cloning or subcloning desired nucleic acid molecules comprising:

(a) forming a mixture by combining *in vitro*

(i) one or more first nucleic acid molecules comprising one or more nucleic acid segments flanked by two or more recombination sites, wherein said recombination sites do not recombine with each other;

(ii) two or more different second nucleic acid molecules each comprising two or more recombination sites, wherein said recombination sites do not recombine with each other;

(iii) at least one recombination protein; and

(iv) at least one [purified] ribosomal protein; and

(b) incubating said mixture under conditions sufficient to transfer one or more of said desired segments into said different second nucleic acid molecules, thereby producing two or more different third nucleic acid molecules.

31. (Three times amended) A method for <u>enhancement of</u> recombinational cloning of one or more desired nucleic acid molecules comprising:

(a) forming a mixture by mixing *in vitro* one or more [of said] desired <u>first</u> nucleic acid molecules with one or more [vectors] <u>second nucleic acid molecules</u> and with at least one [purified] ribosomal protein and an effective amount of at least one recombination protein; and

(b) incubating said mixture under conditions sufficient to transfer said one or more desired <u>first</u> nucleic acid molecules into one or more of said [vectors.] <u>second nucleic acid molecules.</u>

40. (Three times amended) A method for enhancement of recombinational cloning, comprising contacting at least [two nucleic acid molecules] <u>a first nucleic acid molecule and at least a second nucleic acid molecule,</u> each comprising at least one recombination [site] <u>site,</u> *in vitro* with one or more [purified] ribosomal proteins and with one or more recombination proteins to form a mixture, and incubating said mixture under conditions favoring the production of at least one product nucleic acid molecule.

104. (Once amended) The method of [any one of claims 14, 15, 19, 31 and 40,] claim 15, wherein said fourth nucleic acid molecule is a Vector Donor nucleic acid molecule.